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VACTERL-Hydrocephaly, DK-Phocomelia, and Cerebro-Cardio-Radio-Reno-Rectal Community

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Phenotypic manifestations of the autosomal recessive form of VACTERL-hydrocephaly syndrome (David-O'Callaghan syndrome) and the X-linked recessive form (Hunter-MacMurray) syndrome are almost identical. The absence of cardiovascular malformations in cases with undoubtedly X-linked inheritance may be the only exception. The comparison of patients with David-O'Callaghan syndrome and nonclassified sporadic cases of VACTERL-hydrocephaly showed two marked differences. First, radial involvement (usually bilateral) occurred in all familial but only in 22 of 36 sporadic cases. Therefore, radial noninvolvement may be evidence against a genetic origin of the complex in a sporadic case. Second, predominantly severe forms of cardiovascular malformations were found in cases of David-O'Callaghan syndrome, whereas in sporadic cases almost all cardiovascular malformations were simple defects with minimal, if any, hemodynamic disturbances.

The similarity of the spectrum and frequency of main manifestations of David-O'Callaghan and von Voss-Cherstvoy syndromes allows us to think that both of these syndromes actually might be 2 forms of one genetic entity. There are some syndromes with abnormalities of the brain (different for each syndrome) sharing the same limb defects (mainly preaxial), congenital heart defects, abnormalities of kidneys, and anal atresia/ectopia. Baller-Gerold syndrome, Steinfeld syndrome, XK-aprosencephaly, and DK-phocomelia (von Voss-Cherstvoy) syndrome as well as Mendelian forms of VACTERL-hydrocephaly syndromes fit into this "cerebro-cardio-radio-reno-rectal community." Am. J. Med. Genet. 70:144–149, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: multiple congenital abnormalities; brain; abnormalities; radius; abnormalities

INTRODUCTION

The combination of hydrocephaly and VACTERL complex (sometimes called VACTERL-hydrocephaly or VACTERL-H syndrome) has been reported in more than 50 cases. Actually, this is a rather heretogeneous group, and the 2 Mendelian syndromes (an autosomal recessive and an X-linked recessive) delineated in this group [Genuardi et al., 1993; Wang et al., 1993] do not cover all cases. In most familial cases, the type of inheritance can be obtained from the pedigree data. For the sporadic cases this decision is not easy.

The purposes of this study are phenotypic comparisons of 1) the autosomal recessive (David-O'Callaghan) and X-linked recessive (Hunter-MacMurray) forms of VACTERL-association and hydrocephaly; 2) David-O'Callaghan syndrome and sporadic cases of VACTERL-H; 3) David-O'Callaghan syndrome and von Voss-Cherstvoy syndrome.

MATERIALS AND METHODS

VACTERL-H was identified in 2 female infants of the Baltimore-Washington Infant Study (BWIS) [Ferencz et al., 1993].

No. 3396

This white girl was the result of the second pregnancy of a healthy 20-year-old mother. The father, 23 years old, reportedly had "a hole in the heart" in infancy. Birthweight was 2,550 g and she had hydrocephaly, tracheo-esophageal fistula, multiple vertebral and rib abnormalities, ventricular septal defect, thrombocytopenia, hypoplastic left lung, absent radius, hypoplastic ulna and rudimentary thumb on the right, and hypoplasia of radius, ulna, and thumb on the left. Her karyotype was 46,XX. The infant died at 10 days. No autopsy was performed.

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No. 3656

This black girl was the result of the second pregnancy of a young couple. Birthweight was 4,160 g and she had hydrocephaly, atrial septal defect, anal atresia, coccygeal abnormalities, and absence of the radii. Ventriculoperitoneal shunting and surgery for anal atresia were performed in the first days of life. At age 1 year she was alive.

Because both of these girls had hydrocephaly plus 4 main manifestations of the VACTERL association (vertebral, radial, and cardiac defects in both cases, tracheo-esophageal fistula in the first case, and anal atresia in the second case), they fit the diagnosis of VACTERL-H.

All available published cases with and characteristic manifestations of the VACTERL association (independent of diagnoses proposed by the authors) were included in this study. Sex of a patient and the presence (or absence) of hydrocephaly (H), cleft palate (CP), significant ear abnormalities, congenital heart defects (CHD), tracheo-esophageal (TE), limb (L), kidney (K), duodenal (D), and rectal (R) defects were noted for each case. Limb defects were subdivided into bilateral (B) and unilateral (U) groups. The presence of hydrocephaly in at least one affected relative with manifestations characteristic of VACTERL-H was considered the minimal criterion to interpret these as familial cases.

Familial cases of VACTERL-H syndrome were subdivided into 3 groups:

1. Six sibships where at least one of the affected sibs was female were classified as autosomal recessive form, although in one of these families [Toriello et al., 1993] no phenotypic details about the affected sib were presented.

2. Two families [Hunter and MacMurray, 1987; Evans et al., 1989 (case 8); Wang et al., 1993; Genuardi et al., 1993] showed a typical X-linked recessive inheritance pattern. In the first of these families, 2 brothers, a maternal uncle, and the son of a maternal sister were affected. In the second family, abnormalities were evident in a propositus and his cousin. The unaffected mothers of these patients were sisters.

3. Two brothers were affected in each of 3 other families [Briard et al., 1984; Froster et al., 1996; Rossbach et al., 1996]. Both autosomal recessive and X-linked recessive inheritance may be proposed in these 3 families.

RESULTS AND DISCUSSION

Comparison of Manifestations in Patients With Autosomal Recessive and X-Linked Recessive Forms

In the first step, phenotypic manifestations of 6 cases with uncertain inheritance [Briard et al., 1984; Froster et al., 1996; Rossbach et al., 1996] were compared with the undoubtedly autosomal recessive and X-linked recessive subgroups (Table I). The general spectrum of abnormalities is the same in all subgroups. There were no significant differences in the spectrum or frequency of abnormalities in subgroups A (autosomal recessive) and B (familial cases of uncertain inheritance). The

TABLE I. VACTERL-H Syndromes: Main Manifestations in Familial Cases

Reference	Sex	H	TE	CHD	CP	Ear	L	K	D	A
Familial cases with autosomal inheritance										
1. David and O'Callaghan, 1975 (1)	F	–	+	–	+	+	+B	–	+	+
2. David and O'Callaghan, 1975 (2)	?	+	–	–	–	+	+B	+	–	+
3. Sujansky and Leonard, 1983 (1)	F	+	+	+	–	–	+B	+	–	–
4. Sujansky and Leonard, 1983 (2)	?	?	+	?	–	–	+B	+	–	–
5. Sujansky and Leonard, 1983 (3)	?	+	–	–	–	–	+B	+	–	–
6. Toriello et al., 1993	F	+	+	+	–	–	+B	+	–	–
7. Evans et al., 1994a (1)	M	–	–	–	+	–	+B	+	+	+
8. Evans et al., 1994a (2)	F	+	–	–	–	–	+B	+	–	–
9. Evans et al., 1994a (3)	F	+	–	–	–	–	+B	+	+	–
10. Evans et al., 1994a (4)	F	+	–	–	–	–	+?	+	+	–
11. Evans et al., 1994b (1)	F	+	–	+	–	–	+B	–	–	+
12. Evans et al., 1994b (2)	F	–	–	+	–	–	+U	+	–	+
		8/11	4/12	4/11	2/12	2/12	12/12	10/12	4/12	5/12
Familial cases with uncertain inheritance										
1. Briard et al., 1984 (1)	M	+	+	+	–	+	+B	+	?	–
2. Briard et al., 1984 (2)	M	+	+	+	–	+	+B	+	?	–
3. Froster et al., 1996 (1)	M	+	–	+	+	+	+B	+	–	+
4. Froster et al., 1996 (2)	M	+	–	–	–	+	+B	–	–	–
5. Rossbach et al., 1996 (1)	M	+	–	+	–	–	+U	+	–	+
6. Rossbach et al., 1996 (2)	M	±	–	+	–	–	+B	?	–	+
		6/6	2/6	5/6	1/6	4/6	6/6	4/5	0/4	3/6
Familial cases with X-linked recessive inheritance										
1. Hunter and MacMurray, 1987 (1)	M	+	+	–	+	–	+B	+	–	+
2. Hunter and MacMurray, 1987 (2)	M	+	–	–	–	–	+B	+	–	+
3. Evans et al., 1989 (8)	M	+	?	?	?	?	+B	?	?	?
4. Wang et al., 1993	M	+	?	?	?	?	+B	+	?	–
5. Genuardi et al., 1993 (1)	M	+	+	–	+	–	+B	+	+	+
6. Genuardi et al., 1993 (2)	M	+	–	–	+	–	+B	+	–	+
		6/6	2/4	0/4	3/4	0/4	6/6	5/5	1/4	4/5

only difference between subgroups B and C (X-linked recessive inheritance) appears to be the cardiovascular malformations which were found in 5 of 6 patients in subgroup B, but were not detected in subgroup C ($t = 2.58$; $P < 0.01$). All other differences were not significant. Therefore, it seems more likely that patients from subgroup B actually belong to the autosomal recessive subgroup, although X-linked inheritance cannot be completely excluded. The combined data on subgroups A and B were used for further comparison.

Comparison of Manifestations in the Autosomal Recessive Form and in Sporadic Cases of VACTERL-H

There are 36 sporadic cases of the VACTERL-H (Table II). In 3 cases the sex of the infant was not reported, 17 patients were females, and 16 were males. Therefore, the proportion of an X-linked recessive form among sporadic cases does not seem to be significant.

All defects under study were encountered in sporadic and familial cases. Most abnormalities occurred with the same frequency in both groups of patients. Limb defects (including radial and/or thumb a/hypoplasia) were found in all 18 familial cases, but only in 22 of 36 sporadic cases. The difference is significant ($t = 3.07$; $P < 0.01$). Bilateral limb defects were mentioned in 15 of 17 familial and in 17 of 35 sporadic cases (the laterality was not reported in one patient from each group).

There are significant differences in the spectrum of cardiovascular malformations (CVM) in familial cases of the autosomal recessive form and in sporadic VACTERL-H cases. In the autosomal recessive subgroup, 3 of 9 CVM were not specified, one patient had a ventricular septal defect which closed spontaneously, and 5 patients had severe defects with potentially significant hemodynamic disturbances: atrioventricular communication [Toriello et al., 1993], atresia of pulmonary artery and tricuspid atresia [Evans et al., 1994b], truncus arteriosus [Evans et al., 1994b; Rossbach et al., 1996], and Eisenmenger complex [Froster et al., 1996]. Evidently, serious CVM prevail in this syndrome. In sporadic VACTERL-H cases, the type of CVM was not specified in 4 of 20 cases. Among the 16 other patients, only one [Cochrane et al., 1985] had transposition of great arteries, whereas 15 patients had simple defects with potentially minor hemodynamic abnormalities. The difference is significant. If these findings hold true, the type of CVM may be another criterion which helps to diagnose the autosomal recessive cases.

Therefore, limb defects (especially bilateral) and severe CVM might be the indirect evidence for the genetic origin of a complex. More importantly, *absence* of

TABLE II. VACTERL-H: Main Manifestations in Sporadic Cases

Reference	Sex	H	TE	CHD	CP	Ear	L	K	D	A
1. Baumann et al., 1976	F	+	+	–	–	–	+U	+	–	+
2. Russell et al., 1981	M	+	–	+	–	–	–	+	–	+
3. Carlo et al., 1982	M	+	–	+	–	–	–	+	–	+
4. Aleksic et al., 1984	M	+	+	–	–	–	+B	+	–	+
5. Briard et al., 1984 (3)	F	+	+	+	–	–	+B	–	?	+
6. Briard et al., 1984 (4)	M	+	–	+	–	–	+B	+	?	+
7. Briard et al., 1984 (5)	F	+	+	–	–	–	+B	+	?	+
8. Briard et al., 1984 (6)	M	+	–	+	–	–	+B	+	?	+
9. Briard et al., 1984 (7)	F	+	+	–	–	+	+B	+	?	–
10. Briard et al., 1984 (8)	F	+	+	–	–	+	+U	–	?	+
11. Briard et al., 1984 (12)	M	+	–	–	–	–	–	+	?	+
12. Briard et al., 1984 (14)	M	+	–	–	–	–	–	+	?	+
13. Briard et al., 1984 (15)	M	+	–	–	–	–	+B	–	?	+
14. Briard et al., 1984 (16)	F	+	+	+	–	–	–	+	?	+
15. Cochrane et al., 1985	?	+	–	+	+	+	+?	–	+	–
16. Milstein et al., 1985	?	+	+	+	–	–	+U	–	–	–
17. Vintzileos et al., 1987	?	+	+	+	–	+	–	–	–	+
18. Evans et al., 1989 (1)	F	+	–	+	–	–	–	+	–	+
19. Evans et al., 1989 (2)	F	+	–	+	+	+	+B	+	–	+
20. Evans et al., 1989 (4)	F	+	+	+	–	–	+B	–	–	–
21. Evans et al., 1989 (5)	F	+	+	+	–	–	–	+	+	+
22. Evans et al., 1989 (6)	F	+	+	+	–	–	–	+	–	–
23. Evans et al., 1989 (7)	M	+	–	–	–	–	+B	+	–	+
24. Iafolla et al., 1991 (1)	M	+	–	+	–	–	+B	+	–	+
25. Iafolla et al., 1991 (2)	M	+	–	+	–	–	–	+	–	+
26. Iafolla et al., 1991 (3)	F	+	+	+	–	–	–	+	–	+
27. Örstavik et al., 1992	F	+	–	–	–	–	–	+	–	+
28. Porteous et al., 1992 (1)	M	+	–	–	–	–	+B	+	–	–
29. Porteous et al., 1992 (2)	M	+	+	–	–	–	+B	+	–	–
30. Sorge et al., 1992	M	+	+	+	–	–	–	+	–	–
31. Toriello et al., 1993	M	+	+	–	–	–	+B	+	–	+
32. Vandenborne et al., 1993 (1)	M	+	–	–	–	–	+U	+	–	–
33. Vandenborne et al., 1993 (3)	F	+	+	–	–	–	–	+	+	+
34. Evans et al., 1994b	F	+	+	–	–	–	+B	+	–	+
35. BWIS, no. 3396	F	+	+	+	–	–	+B	?	–	–
36. BWIS, no. 3656	F	+	–	+	–	–	+B	?	–	+
			19/36	20/36	2/36	5/36	22/36	27/34	3/26	27/36

radial defects is strong evidence *against* Mendelian syndromes, because radial defects were found in *all* familial cases, including 13/13 sibs and other affected relatives of the propositi.

No finding is an obligate manifestation of any Mendelian syndrome. Although in the sporadic group hydrocephaly was a prerequisite for patient selection, in the autosomal recessive group there are 3 sibships [David and O'Callaghan, 1975; Evans et al., 1994a, b] where only one of the affected sibs had hydrocephaly, and 2 [Sujansky and Leonard, 1983; Evans et al., 1994a] where both sibs had this defect. Therefore, as to be expected, hydrocephaly may be lacking in some patients with the autosomal recessive VACTERL-H syndrome. Therefore, it would be better to avoid this term at least for the autosomal recessive form of the syndrome. We propose the eponym "David-O'Callaghan syndrome," because David and O'Callaghan [1975] first described sibs with this entity.

Some patients with David-O'Callaghan syndrome were described as severe cases of the Fanconi anemia (FA). All of these patients had chromosome breaks, typical of FA, especially when cultures were exposed to mitomycin C. Surprisingly, these aberrations were found not only in the autosomal recessive form [Toriello et al., 1993; Evans et al., 1994a], but also in the definite X-linked recessive form [Wang et al., 1993]. Therefore, this form of breakage is not pathognomonic for any syndrome, but is a common (although rather specific) phenotypic (not genotypic!) manifestation of some entities sharing common (or related) metabolic defect(s). The excessive chromosomal breakage is hardly enough for the diagnosis of FA in these patients. Moreover, if hydrocephaly, anal atresia, and kidney defects really are rare manifestations of FA, an increased rate of these malformations in sibs of index cases with classic FA would be expected. But this has not been found to be so [Glanz and Fraser, 1982].

David-O'Callaghan Syndrome, von Voss-Cherstvoy Syndrome, and Cerebro-Cardio-Radio-Reno-Rectal "Community"

DK-phocomelia (von Voss-Cherstvoy syndrome) [Lubinsky et al., 1994] comprises occipital encephalocele (OE) and a group of malformations similar to those of VACTERL-H (Table III). The comparison of the frequency of abnormalities in familial forms of VACTERL-H and in the DK-phocomelia syndrome shows the same spectrum and frequency of all studied congenital defects in both groups.

OE was a prerequisite for the diagnosis of the entity in sporadic cases. Only 2 sibships with this supposedly autosomal recessive syndrome have been reported [Froster-Iskenius and Meinecke, 1992; Kunze et al., 1992], and OE was absent in 2 of 3 sibs (although various brain defects were present). The third family [Bird et al., 1994] is very unusual: A female fetus had OE, cleft palate, absence of the left radius, horseshoe kidney, anal atresia (all typical findings of von Voss-Cherstvoy syndrome), and diaphragmatic agenesis. Omphalocele, diaphragmatic agenesis, and polysplenia, but no manifestations of the DK-phocomelia syndrome, were found in her brother. That is why only the female index case was included in our analysis.

Two apparently different multiple congenital anomalies (MCA) syndromes share the same combination of congenital defects. The only difference is the brain anomaly—hydrocephaly or OE. This similarity allows us to suppose that these syndromes may be different manifestations of the same entity. Some formal evidence supports this hypothesis. Thrombocytopenia, found in some patients with the DK-phocomelia syndrome [von Voss et al., 1979], may occur in some patients with David-O'Callaghan syndrome as well [Evans et al., 1994a]. OE is a characteristic manifestation in some MCA syndromes, including Meckel and Walker-Warburg syndromes. In some families, one affected sib with these syndromes had OE, and another

TABLE III. Main Manifestations in the Patients With DK-Phocomelia Syndrome

Reference	Sex	OE	TE	CHD	CP	Ear	L	K	D	A
1. Fried et al., 1974	F	+	–	+	–	–	+B	–	–	–
2. Baumann et al., 1976 (3)	F	+	+	–	+	–	+B	+	–	–
3. Von Voss et al., 1979	F	+	–	+	–	–	+B	+	–	–
4. Cherstvoy et al., 1980	M	+	–	–	–	–	+B	+	–	–
5. Kahler, 1983	M	+	–	+	–	+	+B	+	–	–
6. Evans et al., 1989 (3)	M	+	–	+	–	–	–	+	–	–
7. Froster-Iskenius and Meinecke, 1992 (1)	F	+	+	+	–	–	+B	–	–	+
8. Froster-Iskenius and Meinecke, 1992 (2)	F	+	–	+	+	+	+B	+	–	+
9. Kunze et al., 1992 (1)	M	+	+	+	–	–	+B	+	+	+
10. Kunze et al., 1992 (2)	M	–	–	–	–	–	+B	–	–	–
11. Kunze et al., 1992 (3)	M	–	–	+	–	–	+B	+	–	–
12. Bird et al., 1994	F	+	–	–	+	–	+U	+	–	+
13. Corsello and Giuffre, 1994	M	+	+	+	+	–	+B	+	–	+
14. Lubinsky et al., 1994 (2)	F	+	–	–	–	–	+B	+	–	–
15. Lubinsky et al., 1994 (3)	F	+	–	+	–	–	+B	+	+	+
16. Lubinsky et al., 1994 (4)	F	+	–	–	–	–	+B	+	+	+
17. Schüler and Salzano, 1994 (19)	?	+	?	+	–	+	+B	?	?	+
18. Urioste et al., 1994	M	+	–	–	–	+	+B	–	–	–
19. Lin et al., 1996	F	+	–	–	–	–	+U	+	–	–
		17/19	4/18	11/19	4/19	4/19	18/19	14/18	3/18	8/19

TABLE IV. The Cerebro-Cardio-Radio-Reno-Rectal Community: Frequency of Common Manifestations*

Syndrome	CHD	CP	Ear	Radial defects	Kidney	Anus
David-O'Callaghan	8/15	2/16	4/16	16/16	13/15	5/12
Von Voss-Cherstvoy	11/19	4/19	4/19	18/19	14/18	8/19
Baller-Gerold	5/22	2/22	4/22	22/22	5/22	9/22
XK-aprosencephaly	3/7	0/7	2/7	6/7	1/7	3/7
Steinfeld	2/7	4/7	1/7	6/8	3/5	0/7

*The review article [Lin et al., 1993] and some additional publications [Nwokoro et al., 1993; Reichenbach et al., 1993; Van Maldergem et al., 1992] were used for the calculations for the Baller-Gerold syndrome. The data about XK-aprosencephaly syndrome were taken from Townes et al. [1988], Kim et al. [1990], and Pauli [1992]. Only 2 families with Steinfeld syndrome have been reported [Steinfeld, 1982; Nöthen et al., 1993]. Neither reported patient with Baller-Gerold, Steinfeld, and XK-aprosencephaly syndromes had esophageal or duodenal atresias.

one had hydrocephaly [Anderson, 1982; Rodgers et al., 1994]. If so, OE and hydrocephaly may be different manifestations of the same embryonal abnormality.

Certainly, a primary study of mutations or sibship where one sib will have OE (+ other manifestations) and another one will have hydrocephaly (+ other manifestations) could provide the answer. All other arguments are indirect and cannot be final. Nevertheless, a noteworthy closeness between von Voss-Cherstvoy syndrome and David-O'Callaghan syndrome deserves thorough study by clinicians, cytogeneticists, and molecular geneticists.

An association of abnormalities of the brain, radial structures, heart, kidneys, and rectum is not random. An entire community of cerebro-cardio-radio-renorectal syndromes can be delineated. Autosomal recessive Baller-Gerold syndrome [Lin et al., 1993], supposedly autosomal recessive XK-aprosencephaly [Kim et al., 1990] and autosomal dominant Steinfeld syndrome [Nöthen et al., 1993], may fit into this community as well as David-O'Callaghan and von Voss-Cherstvoy syndromes. As a rule, the nosologic diagnosis of other entities which fit into the cerebro-cardio-radio-renorectal community is not so difficult (Table IV). Although all of these syndromes share some common malformations, the anal and renal defects in Baller-Gerold, Steinfeld, and XK-aprosencephaly syndromes are less frequent, and so far no reported patient with these forms had tracheo-esophageal or duodenal abnormalities.

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